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3M

By Courier
October 28, 2003

MR 270574

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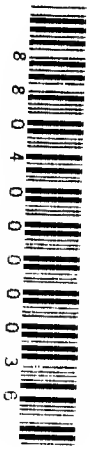
Document Processing Center – CBIC (7407M)
Room 6428 East / Phone 202-564-8940
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
US Environmental Protection Agency
1201 Constitution Avenue NW
Washington DC 20460-0001

RE: TSCA 8(E) SUBSTANTIAL RISK NOTICE ON: 1-Butanesulfonamide, 1,1,2,2,3,3,4,4,4-nonafluoro-n-methyl ('N-MePFBA') [CAS 68298-12-4]

Dear Sir/Madam:

3M has received preliminary data for a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test in rats conducted with a chemical intermediate, 1-Butanesulfonamide, 1,1,2,2,3,3,4,4,4-nonafluoro-n-methyl [CAS 68298-12-4] (N-MePFBA) indicating reproductive and possible neurotoxic effects.

The study was conducted by Notox Safety and Environmental Research. Male rats were orally administered N-MePFBA at doses of 0, 50, 150 or 1000 mg/kg/day beginning fourteen days before cohabitation and continuing until after cohabitation, for a minimum of 28 days of dosage. Female rats were orally administered the substance at the same dosage levels beginning fourteen days before cohabitation and continuing until day 5 of lactation.



In the 1000 mg/kg/day dosage group, several significant reproductive effects were observed. Of the nine mated females, only four pregnancies occurred and only three litters were produced. Consequently, there was a decreased fertility index, conception rate, and gestation index in this group. Treatment-related post natal-loss was reported. Mean body weights in the pups were decreased on days 1 and 4 during lactation. Macroscopic examination of the pups revealed small appearance, no milk, and cannibalism.

Additionally, male and female rats in the 1000 mg/kg/day dosage group were observed to display adverse clinical signs including lethargy, hunched posture, uncoordinated movements, decreased locomotor activity, quick breathing, labored respiration, rales, shallow respiration, and salivation, which may indicate neurotoxic effects.

N-MePFBA is used as a chemical intermediate. 3M believes that human and environmental exposure to this material is very low.

N-MePFBA is present in final products as an impurity at a level restricted to less than 0.1 percent according to manufacturing specifications. Workplace exposure within 3M is carefully controlled through our EHS management systems.

A copy of the final report will be forwarded to EPA when received.

Please contact Paul Lieder (651-737-2678) if you have any questions or if we can provide additional information.

Once a docket number has been assigned for this submittal, please send the docket number postal card to Cheri Kedrowski, 3M Center Bldg. 220-2E-02, St. Paul, MN 55144.

Sincerely,

Katherine E. Reed

Katherine E. Reed
Staff Vice President, Environmental Technology and Safety Services

270574

STATUS REPORT

COMBINED REPEATED DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST WITH T-7601 ADMINISTERED BY ORAL GAVAGE IN WISTAR RATS

NOTOX Project 385717
NOTOX Substance 113769/B

SUMMARY OF RESULTS

Study start:	21 July 2003
Start mating:	04 August 2003
Necropsy of males	18 August 2003
Delivery of litters	27 to 31 August 2003
Necropsy of females and pups	01 to 05 September 2003

Allocation:

Group	Dose level mg/kg b.w./day	Number of animals		Animals numbers	
		F_0 males	F_0 females	males	females
1	0	10	10	01-10	41-50
2	50	10	10	11-20	51-60
3	150	10	10	21-30	61-70
4	1000	10	10	31-40	71-80

MORTALITY

Group 1: No mortality.
Group 2: No mortality.
Group 3: Female 65 was killed in extremis due to prolapse of the uterus just after delivery.
Group 4: Male 33 was found dead on day 12 of treatment. Male 34 was found dead on day 7 of treatment. Male 38 was killed in extremis on day 24 of treatment. Female 77 was killed in extremis on day 14 of treatment. Female 78 was found dead on day 29 of treatment.

CLINICAL SIGNS

Treatment related clinical signs were noted in the mid dose group (150 mg/kg) and the high dose group (1000 mg/kg).
At 1000 mg/kg, these consisted of lethargy, hunched posture, uncoordinated movements, decreased locomotor activity, quick breathing, laboured respiration, rales, swallow respiration, swelling of the genital region and abdomen, piloerection, red discolouration of urine, diarrhoea, salivation, chromodacryorrhoea of the eye and snout, lean appearance and ptosis.
At 150 mg/kg, these consisted of salivation and diarrhoea.

Rales and salivation were also observed in the other groups, however at a much lower incidence. Alopecia was observed at a low incidence at 150 and 1000 mg/kg, This is within the limits of historical control data of rats of this strain and age that are housed and treated under the conditions of this study.

FUNCTIONAL OBSERVATIONS

No changes were observed in hearing ability, papillary reflex, static righting reflex and grip strength in the treated animals, when compared to control animals.

The variation in motor activity did not indicate a relation with treatment.

BODY WEIGHTS

Body weights and body weight gain of males of the 1000 mg/kg dose group were statistically significantly decreased during treatment. Several males in this group also showed severe body weight loss.

Females of the highest dose group showed statistically significantly decreased body weights and body weight gain during the pre-mating period. Three females also showed a body weight loss in this period. Body weights of females of the highest dose group were also decreased during pregnancy and lactation. This decrease was not statistically significant due to the limited number of females in this group.

No treatment related effects on body weights and body weight gain were observed at 50 and 150 mg/kg body weight/day.

FOOD CONSUMPTION

Food consumption and relative food consumption were decreased during the complete treatment period. Statistical significance was reached for food consumption and relative food consumption during pre-mating (male and female), and for food consumption during post-mating (males) and lactation (females).

No treatment related effect on food consumption and relative food consumption were observed at mid and low dose groups.

HAEMATOLOGY

The following statistically significant differences of haematology parameters were recorded in the highest dose group at the end of treatment:

- increased erythrocytes count (males and females)
- increased haemoglobin concentration (males and females)
- increased haematocrit (males and females)
- increased mean corpuscular volume (males)
- increased mean corpuscular haemoglobin (males)
- increased mean corpuscular haemoglobin concentration (males)
- increased red cell distribution width (males).

These findings were considered to be treatment related.

In the 50 mg/kg dose group a statistically significantly increase for platelets count in females was recorded. As no dose relationship was observed, this finding was considered to be caused by chance.

No other statistically significant effects upon haematology parameters were noted.

CLINICAL BIOCHEMISTRY

The following statistically significant differences of clinical biochemistry parameters were recorded in the highest dose group at the end of treatment:

- increased alanine aminotransferase (males)
- increased alkaline phosphatase (males)
- increased urea (males)
- increased triglyceride (males)
- increased chloride (males)
- increased inorganic phosphorus
- decreased aspartate aminotransferase (females)
- decreased bilirubin (females)
- increased albumin (females).

These findings were considered to be treatment related.

Inorganic phosphorus was decreased in all treatment groups to the same extent. Since no dose-relationship or correlative findings were noted, the inorganic phosphorus decrease was considered to be of no toxicological significance.

MACROSCOPIC FINDINGS

At necropsy, respectively, three, four, seven and fifteen animals (out of twenty animals) in the control, 50, 150 and 1000 mg/kg dose groups were affected.

Four males in the highest dose group appeared to have yellowish nodule(s) on the epididymides. This finding was not observed in the other groups. Histopathology, that has not been performed yet, should reveal whether this finding is of toxicological significance.

Three animals of the 1000 mg/kg dose group died spontaneously. Male 33 was partly cannibalised and showed isolated dark red focus on the thymus, dark red discolouration of lungs and left mandibular lymphnode. Male 34 was partly cannibalised, showed beginning autolysis, reddish discolouration of the stomach and many dark red foci on both sides of the thymus. Female 78 showed dark red discolouration of the mesenteric lymph node and the left adrenal gland grown together with the kidney.
Two animals of the 1000 mg/kg group were killed in extremis. Male 38 was emaciated, showed a thickened limiting ridge of the stomach, an irregular surface of the fore stomach, reddish discoloured caecum, accentuated lobular pattern of the liver, enlarged liver and dark red contents of the urinary bladder. Female 77 was emaciated and showed a fore stomach with many crateriform retractions.
In the 150 mg/kg dose group, female 65 was killed in extremis and showed a prolapse of the uterus.

Incidental findings that were observed in the highest dose group included pelvic dilation of the kidney(s), reddish discolouration of the duodenum, watery-clear cysts on the uterus, reddish discolouration of the thymus, dark red discolouration of right mandibular lymph node.
Incidental findings observed in the other groups consisted of isolated/many dark red foci on the thymus, several reddish foci on thymus, light red discolouration of the thymus, dark red discolouration of the liver and right mandibular lymph node, accentuated lobular pattern of the liver, pelvic dilation of the kidney(s), alopecia in throat region, isolated/several gray-white foci on adrenal glands, exophtalmus of right eye, constricted spleen and several tan foci on the clitoral glands.
These finding are observed in rats of this age and strain that are housed and treated under the conditions of this study. At the incidence observed, these signs were therefore considered to be of no toxicological significance.

The finding of an uterus containing fluid, was noted for female 71 and 79 of the highest dose group. This finding is related to an oestrous cycle stage and therefore a physiologic finding.

ORGAN WEIGHTS

In the highest dose group, males showed statistically significantly decreased body weights and thymus weights at necropsy. Relative organ weights of brain, heart, liver, spleen, testes, and epididymides were statistically significantly increased.
The female body weights of this group were also statistically significantly decreased, and their absolute and relative liver weights and relative heart weights were statistically significantly increased.
These aberrations could be caused by the reduced body weights, however, for a correct interpretation we have to take the histopathologic results into account. Unfortunately, these are not available yet.

No statistical significant differences in organ weights were observed in 50 and 150 mg/kg dose groups.

MICROSCOPIC EXAMINATION

No results available yet.

REPRODUCTION

Table I. Reproduction Data

Number of females	Group 1 Control	Group 2 50 mg/kg	Group 3 150 mg/kg	Group 4 1000 mg/kg
Paired	10	10	10	9
Mated	10	10	10	9
Pregnant	10	9	8	4
Litters with living pups	10	9	8	3

All females mated within four days of pairing.

Reproduction of females of the 1000 mg/kg dose group was negatively affected. This was shown by four pregnancies out of nine mated females. One of these pregnant females (female 78) died spontaneously on day 12 *post-coitum*; at necropsy this female showed implantation sites after Salewski staining. As a result only three litters with living pups were recorded in this group. This gave rise to a decreased fertility index, conception rate and gestation index in the highest dose group.

Reproduction parameters up to 150 mg/kg body weight/day were found to be within normal limits.

BREEDING DATA

Duration of gestation was not affected by treatment.

In all treatment groups, postnatal loss was statistically significantly increased. This resulted in a statistically significantly decreased viability index for all treatment groups. However, these findings were considered unrelated to treatment at 50 and 150 mg/kg, and are difficult to asses at 1000 mg/kg.
At 50 and 150 mg/kg, increased postnatal loss was mainly due to the loss of one complete litter (consisting of 13 pups at 50 mg/kg and 5 pups at 150 mg/kg), and as the number of living pups on day 4 of lactation was considered to be normal, the changes in postnatal loss and viability index were regarded to be unaffected by the test item at these dose levels.
At 1000 mg/kg, it is difficult to assess breeding data as this group consists of only 3 litters. However, there seems to be a tendency for poor breeding performance regarding postnatal loss between days 0 to 4 post partum.

PUPS

Mean body weights of pups per group in the highest dose group were statistically significantly decreased on days 1 and 4 during lactation.

In the 50 mg/kg dose group, statistically significantly decreased body weights were measured on day 1 (female pups) and day 4 (male and female pups). This finding was not considered to be treatment-related, since pup body weights in the control group were very close to the upper limit of historical control data. Moreover, no dose-relationship was noted.

Other effects upon pup body weights during lactation period were not established.

Clinical signs were noted in all groups, but the incidence in the 1000 mg/kg group was slightly increased. Findings consisted of a small, cold or pale appearance, and little or no milk. One pup of the control group showed an absent tail.
Macroscopic examination of pups revealed small appearance, no milk and cannibalism. The incidence of small pups was increased in the highest dose group. This corresponded with the observed decreased body weights in this group.